SUMMARY MINUTES

OF THE

EAR, NOSE AND THROAT DEVICES

ADVISORY PANEL MEETING

OPEN SESSION

July 20-21, 2000

Holiday Inn Gaithersburg
Goshen Room
Gaithersburg, MD

Ear, Nose and Throat Devices Panel Roster
July 20-21, 2000

Carl A. Patow, M.D.
Chair

Gayle E. Woodson, M.D.+
Voting Member

Clough Shelton, M.D.#
Voting Member

Anjum Khan, M.D.
Voting Member

Paul R. Kileny, Ph.D.+
Voting Member

Howard Francis, M.D.
Consultant, deputized to vote

A. Julianna Gulya, M.D.*
Consultant, deputized to vote

Linda J. Hood, M.D.
Consultant, deputized to vote

Ross J. Roeser, Ph.D.*
Consultant, deputized to vote

Alexa J. Canady, M.D.#
Consultant, deputized to vote

William H. Duffell, Jr., Ph.D.
Industry Representative

*Primary Reviewer for PMA P990052
+Primary Reviewer for PMA P000015
#Present only on July 21, 2000

FDA Participants

Sara M. Thornton
Panel Executive Secretary

Nancy C. Brogdon
Acting Director, Division of Ophthalmic and Ear, Nose and Throat Devices

Morris Waxler, Ph.D.
Acting Chief, Ear, Nose and Throat (ENT) Devices Branch

Karen H. Baker, MSN, RN
Nurse Consultant, ENT Devices Branch
Team Leader for PMA P990052

I. Sidney Jaffee, M.D.
Medical Officer, ENT Devices Branch
Clinical Reviewer for PMAs P990052 and P000015

Teri M. Cygnarowicz, M.A., CCC-A
Audiologist, ENT Devices Branch
Audiology Reviewer for PMA P990052
Team Leader for PMA P000015

James K. Kane, Ph.D., CCC-A
Audiologist, ENT Devices Branch
Audiology Reviewer for PMA P000015

Alfred W. Montgomery, D.V.M.
Veterinary Medical Officer
Senior Regulatory Reviewer, ENT Devices Branch

OPEN SESSION—July 20, 2000

Dr. Carl A. Patow, Panel Chair, called the Open Session to order at 9:50 a.m., and introduced **Panel Executive Secretary Sara Thornton**. Ms. Thornton extended a special welcome to new panel consultants Drs. Howard W. Francis and Linda J. Hood, and asked the rest of the panel to introduce themselves. Dr. Patow read the charge to the panel, stating that the purpose of the meeting was to discuss a premarket approval application (PMA) for a middle ear amplification device. Ms. Thornton read the conflict of interest statement, noting that a waiver had been issued to Dr. Kileny for his interest in a firm at issue and that matters concerning Dr. Francis had been considered but deemed not to pose a conflict. Ms. Thornton also read the appointment to temporary voting status for Drs. Francis, Gulya, Hood, and Roeser.

OPEN PUBLIC HEARING

Mr. Lee Richardson spoke as a hearing aid user and from his evaluation of information published by the sponsor. He raised six questions relating to the benefits and advisability of the device for different populations, possible scenarios of risks, inconveniences and costs to users from the procedure and afterwards, the manufacturer's capability to meet customer needs for post-operation service, the sale and distribution of the device by certain hearing aid sellers, and promotion and advertising claims.

Mr. Jose Bedoya, president of Otologics, listed the criteria for evaluating new medical devices such as risks, benefits, trust, and credibility, and discussed two key criteria for comparing performance with a conventional hearing aid and a middle ear implant (MEI). The first is that evaluating the patient with a well-fit, state-of-the-art digital multi-

channel hearing aid that achieves or approximates a typical aided target is essential for establishing a baseline of the best alternative care. He stated that any comparison to an MEI must be derived from a clinical study that uses the same or very similar target gain and fitting strategy and preferably signal processing technologies for both devices. The second criterion is that proper patient selection for MEI benefit depends on good characterization of device performance in terms of electronic amplification parameters such as maximum performance output and gain and variability in the actual output obtained. Appropriate programming and performance of the MEI for a given patient must be verified in the clinic using referenced and calibrated measurement tools. Mr. Bedoya expressed the hope that FDA would consider these issues when reviewing applications for these devices.

Sigfrid D. Soli, of the House Ear Institute, whose way was paid by Otologics, discussed patient selection for middle ear implants. He outlined three issues: output power and gain, techniques and instrumentation, and candidate selection. He concluded that patient selection should be based on empirical information on output power and gain, using existing evaluation procedures similar to those used with hearing aids. Variability of transmission must be taken into account, and great care must be taken with patient selection.

OPEN COMMITTEE DISCUSSION

Nancy Brogdon, Acting Director of the Division of Ophthalmic and Ear, Nose and Throat Devices Branch, gave the division update. She noted that Dr. A. Ralph Rosenthal, the Division Director, is temporarily working on Health Care Financing Administration issues in the Office of Device Evaluation (ODE), and she introduced

Bernard Statland, the new Director of ODE. The Ear, Nose and Throat Branch Chief and former Panel Executive Secretary Harry Sauberman was also working in ODE on special projects including partnerships with other countries. She introduced **Dr. Morris Waxler, Acting Chief of the Ear, Nose and Throat Devices Branch** and the ENT Branch's new reviewer, audiologist **Dr. James Kane.**

Ms. Brogdon noted that three ENT Panel members were finishing their terms, and she presented a letter of appreciation from FDA Commissioner Dr. Jane Henney and a recognition plaque to voting members Drs. Gayle Woodson, Clough Shelton, and industry representative, Dr. William Duffell, Jr..

Dr. Morris Waxler, Acting Chief of the ENT Devices Branch, gave the branch update, in which he introduced branch personnel and two visiting doctors from Canada, who are participating in the international partnering program.

PMA P990052—Symphonix Devices Inc. –Vibrant P and D Soundbridge

Sponsor Presentation

Dr. Michael Crompton, vice president for regulatory and quality assurance of Symphonix Devices, Inc., introduced the presentation and described the sponsoring company and the devices, which are identical systems except for the type of signal processor and the programmers used to fit the devices. Both are direct-drive, implantable middle ear hearing devices for sensorineural hearing loss. Dr. Crompton also described the device components, showed a model, and read the proposed indications for use.

Dr. Thomas Balkany of the University of Miami and a principal investigator for the IDE, reviewed the surgical procedure used for implantation and discussed the

device's safety profile. He listed two surgical considerations: that the approach has elements similar to those used for cochlear implants and that attachment of the floating mass transducer has elements similar to those used for middle ear prostheses. The safety profile for the device showed a low incidence of adverse events in the clinical trial and those in general were in line with otologic surgery. He concluded that the surgical procedure to implant the Soundbridge is well understood and similar to other otologic procedures and that the incidence of adverse events in the trial was low and clinically acceptable for an implantable middle ear hearing device.

Deborah A. Arthur, vice president for clinical affairs for Symphonix, Ind., described the study design and patient demographics and summarized the proposed labeling claims for the device. She explained that the trial was a traditional single-subject repeated measures study design in which each patient serves as his or her own control. Ms. Arthur described the study intervals for both Vibrant P and Vibrant D Audio Processor and study measures, which included pure-tone air and bone conduction, tympanometry, and word recognition, as well as patient self-assessments. Ms. Arthur explained subject enrollment by phase in the 10 U.S. clinical sites and the selection criteria. Subject demographics were analyzed by years of hearing loss, ear implanted, etiology of hearing loss, and gender. Ms. Arthur also listed the presurgery evaluation of the hearing aid and its appropriateness of fit. .

Ms. Arthur read and discussed the ten specific claims, presenting supporting data on each claim. The safety claim involved changes to unaided hearing threshold; study patients, as a group, did not exhibit a clinically significant shift in residual hearing. Effectiveness claims involved sound quality and clarity, based on patient reports of

satisfaction, and lack of acoustic feedback, and improved fit, also based on patient reports of satisfaction. Language on claims involving functional gain had been modified to state that the device provides equal or increased functional gain compared to the hearing aid, which was based on soundfield functional gain measures. Another group of claims involved patients' perceived benefit with the device in a variety of listening conditions, based on patient results on the profile of hearing aid performance and the Soundbridge Hearing Aid Comparison Questionnaire and the Speech Performance in Noise test, as well as perceived benefit in various listening conditions

Dr. David Fabry, of the Mayo Clinic and a member of the sponsor's Advisory Board, presented audiologic perspectives. He read the proposed indications for use and discussed why an implantable middle ear hearing device is needed. His discussion included changing demographics of the hearing impaired, hearing aid market penetration, and patient satisfaction with hearing aids. After an analysis of the primary reasons for dissatisfaction with hearing aids in the present study, Dr. Fabry looked at expectations of implantable middle ear devices, which include improved sound quality, reduced feedback, comfort, and cosmetics, showing statistics on the percentages of patients who achieved improvement or satisfaction in these areas in the Vibrant clinical studies. He concluded that the Vibrant Soundbridge satisfies an unmet medical need and addresses certain limitations inherent in acoustic devices while increasing perceived patient benefit. .

Panel Questions to the Sponsors

Panel questions to the presenters focused on the stability of the device and the risk of trauma to the device based on activity level of the patient. There was considerable discussion of validation measures and statistical issues, such as appropriateness of

methods and adjustments. Use of the device with assistive listening devices was also an issue, as was the adjustment period. Surgical dimensions included the possibility of revision, the necessary dimensions of facial recess, and the training necessary for the procedure.

FDA Presentation

Dr. Morris Waxler, Acting Chief of the Ear, Nose and Throat Devices Branch, introduced **Ms. Karen Baker, PMA team leader.** Ms. Baker introduced the review team.

Dr. I. Sidney Jaffee gave the clinical review. He focused on the phase III study, which involved 54 patients in the United States and 351 patients worldwide. After modification to correct a design flaw, the phase IIIa study was launched to include 30 patients in the United States and 60 in Europe. Safety results showed some loss in residual hearing for several patients but no device failures after device modification. Adverse events included facial nerve problems, flap complications, irritation or infection, disconnection of the transducer, and altered taste, transient pain or postoperative problems, increased tinnitus, residual hearing loss, and a sensation of fullness. The device had some surgical similarities to stapes surgery in that both groups can usually be helped with hearing aids and some similarities to cochlear implantation, although it is not equivalent because there is no alternative to cochlear implants for profound deafness. Dr. Jaffee noted three major issues: device incompatibility with MRI, the issue of binaurality, and the fact that long-term use may require further surgical procedures. Advantages he listed included the openness of the ear canal, the ease of use, cosmetic effect, and device longevity. Disadvantages included MIR incompatibility, issues with binaurality, device

longevity, and the technical surgical nature of the procedure involving a normal mastoid and middle ear. Dr. Jaffee read the first four discussion questions to the panel.

Ms. Teri M. Cygnarowicz gave the audiology review. She focused her review on the effectiveness data. The first issue she raised involved the choice of control, in which sponsors chose not to fit subjects with a hearing aid circuit similar to that used in the audio processor of the device. It also selected a prescriptive formula for real ear probe microphone testing of the patient's existing hearing aid, whereas it did not incorporate a prescriptive formula to fit the audio processor. Conventional real ear testing is not possible with the device, which may be viewed as a device limitation. She asked for advice regarding labeling as it pertains to the control used in the clinical trial. She also asked for panel input regarding the use of subjective outcome measures as the basis of effectiveness data and resulting claims. Ms Cygnarowicz then read the remaining panel questions for discussion.

Panel Questions to the FDA

There were no panel questions for the FDA presenters.

Additional Comments from the Sponsors

Deborah Arthur and David Fabry commented on the appropriateness of the control selected, saying that sponsors had looked at individual patient data in response to the FDA's concern and still felt that their choice of control was appropriate for real ear use in gauging equivalency across the measures targeted.

Dr. Martin Hyde, a consulting biostatistician for the sponsor, noted the trend toward incorporating psychometrically valid measures into objective evaluation. He stated that the questionnaire used was an exemplary standard of measurement.

Dr. Arthur also stated that the sponsors were not opposed to binaural implantation, but such implantation runs contrary to the current guidelines for clinical studies.

COMMITTEE DELIBERATIONS

Primary Panel Reviews

Dr. A. Julianna Gulya recommended that the PMA be recommended as approvable, subject to various conditions. She approved the clarification made in the intended use statement and reviewed each of the 10 claims. She recommended additional, longer-term follow-up be done on effect on residual hearing, through postmarketing surveillance. Dr. Gulya thought that claims two and three on significant improvement in sound clarity and quality and overall fit and comfort should be altered to reflect the subjective nature of the data. Claims four, five, six, and eight on feedback, functional gain, everyday listening situations, and maintenance issues were supported by the data, in her opinion. Satisfaction in challenging listening environments should be reconsidered; she did not feel the data supported this claim or that of listening to speech in various listening situations. Claim 10 regarding improvement in recognition in background noise as compared to unaided condition should be reworded. Dr. Gulya also agreed on the significance of restrictions on MRI testing and included cautions regarding cell phones. She though it reasonable to require language regarding the importance of binaural hearing and to recommend that the implanted individual should strongly consider hearing aid evaluation and fitting in the unimplanted ear. She agreed with the medical review that patients should be counseled regarding surgical risk and longevity. Adverse events were

not worrisome or undue in her opinion. Dr. Gulya also provided her answers to FDA questions for panel discussion.

Dr. Ross Roeser stated in his panel review that the device is an exciting development. He expressed discomfort with the small sample size and subjective data presented and with the intended use as worded, in particular the subjective evaluation of benefit by the patient. In particular he questioned the criteria used to determine that the subjects were receiving a perceived benefit from their hearing aids and whether a patient's lack of perceived benefit might be a result of inadequate hearing instruments or improper fitting. He asked what procedures were used to ensure that the patients studied were wearing appropriately fit, state-of-the-art hearing aids before they were implanted. He thought the key to use of subjective evaluation data is standardization and use of recorded test materials presented with taped recordings.

On the specific claims, Dr. Roeser suggested rewording of the claim relating to residual hearing and provision of additional data. Claims on sound quality and sound clarity and overall fit and comfort should be reworded to reflect that they are based on subjective data and made in comparison to hearing aids. Claims involving functional gain, reduction in acoustic feedback, satisfaction in everyday listening situations, and maintenance were acceptable, with minor rewording. Claims involving perceived benefit in challenging listening situations, preference over the presurgery hearing aid in listening to speech in various listening situations, and word recognition in presence of background noise compared to unaided condition were not supported by the data, in his opinion.

Panel Discussion of FDA Questions

In discussion of claim number one, the panel suggested the following rewording: "For most subjects, the Vibrant Soundbridge does not significantly affect residual hearing. However, a small percentage of some patients may experience hearing loss." Other safety issues that should be addressed include extrusion of the device, changes in taste sensation, changes in residual hearing over time, and ossicular necrosis over time.

On adverse events, the panel thought that the possibility of facial nerve injury should be mentioned in a way consistent with other middle ear surgery advice and should be added to the patient information brochure.

The panel recommended that the possibility of interference with the device if cellular phones are used should be emphasized more or bolded in the patient information guide. The recommendation that device users not be subjected to MRI or enter an MRI suite should also be bolded consistently throughout.

On data to be collected during the postmarket follow-up period of 18 months, the panel suggested extrusion of the device..

The intended use statement was modified to read, "The Vibrant Soundbridge is indicated for use in adults 18 years of age and older who have a moderate to severe sensorineural hearing loss and desire and alternative to an acoustic hearing aid. Prior to receiving the devices it is recommended that an individual have experience with appropriately fitted hearing aids. In discussion of the implications of the control condition on the intended use and proposed claim, the panel thought the controls were not stringent enough as minimum criteria, but that these were exceeded in the study. The claims were also modified as follows:

Claim number 1: For most subjects, the Vibrant Soundbridge does not significantly affect residual hearing for most patients; however, a small percentage of some patients experienced residual hearing loss.

Claim number 2: Based on subjective responses, the Vibrant Soundbridge significantly improves sound clarity and overall sound quality when compared to hearing aids.

Claim number 3: Patients report that the Vibrant Soundbridge provides better overall fit and comfort when compared to conventional hearing aids.

Claim number 4: unchanged

Claim number 5: The Vibrant Soundbridge provides equal or increased functional gain, compared to a hearing aid.

Claim number 6 (and 7): The Vibrant Soundbridge significantly improves a patient's perceived benefit in many situations such as listening to familiar talkers, ease of communication, reverberation, reduced cues, background noise, aversiveness of sounds, and distortions of sounds. The consensus of the panel was that all these situations should be listed as a whole and not separated out as individual conditions.

Claim number 7 was deleted by the panel.

Claim number 8: unchanged.

Claim number 9: Speech perception test results in a controlled soundfield environment (e.g. Nu-6 word scores, SPIN-low predictability word scores) did not demonstrate a significant mean change in scores between the Vibrant Soundbridge and the hearing aid. However, when listening to speech, the Vibrant Soundbridge was significantly preferred over the presurgery hearing aid in various listening situations.

Claim number 10: The Vibrant Soundbridge provides significant improvement in word recognition in the presence of background noise compared to the unaided condition and is equivalent to the conventional hearing aid condition.

After a discussion of reimbursement and liability issues, the panel agreed that the precautions section of the labeling should contain a statement that "the safety and effectiveness of bilateral implants have yet to be established."

OPEN PUBLIC HEARING

Henry Ileki, director of the American Speech-Language-Hearing Association, echoed the remarks made by Mr. Lee Richardson of the morning. He thought it important to consider the cost/benefit analysis as well, and to remember that the high digital return rate may be related to the higher purchase price. He was curious to see if patient satisfaction rates would be as high if the patient paid for the procedure personally. He also asked whether the device could interface with assistive listening devices and if it obviated the need for them.

FDA CLOSING COMMENTS

FDA representatives asked for clarification on whether the MRI interference issue warranted postmarket surveillance and if it was a serious contraindication. It was noted that there are not many situations in which an MRI is absolutely mandatory, and that the issue does not warrant postmarket surveillance.

SPONSOR CLOSING COMMENTS

Sponsor representatives thanked the panel for its thorough and thoughtful review.

PANEL VOTE AND RECOMMENDATIONS

Ms. Thornton read the panel voting instructions and options.

A motion was made and seconded to recommend the PMA as approvable, subject to the following conditions:

1) The revised intended use statement should be modified to include the requirement that prior to receiving the device, it is recommended that an individual have experience with an appropriately fitted acoustical hearing aid.
2) Claims 1 and 2 should be amended as discussed above.
3) Claim 3 should be altered as discussed above.
4) Claim 5 should be altered as suggested.
5) Claim 7 should be removed.
6) Claim 6 should be revised as discussed above.
7) Claim 9 should be revised as discussed above.
8) Claim 10 should be revised as discussed above.
9) The information packet should include the statement that the safety and effectiveness of bilateral implants has not been established.
10) The manufacturer should be required to follow patients in a postmarketing surveillance for device extrusion.
11) The possibility of facial nerve paralysis/injury and taste disturbance should be added to page 8 of the patient information packet.

The motion to recommend the PMA as approvable subject to all the above conditions carried unanimously. Panel members stated that they voted for approval based on demonstration of safety and efficacy and on the importance of this development as a sign of progress in the field.

Ms. Thornton thanked the sponsors, staff, and panel members, as did Panel Chair Dr. Patow, who adjourned the session for the day.

OPEN SESSION—July 21, 2000

Panel Chair Dr. Patow began the Open Session for the day at 9:15 a.m. **Panel Executive Secretary Sara Thornton** noted that the Consumer Representative for the panel was absent because of illness and asked the rest of the panel to introduce themselves. She read the conflict of interest statement, noting that matters involving Drs. Kileny and Shelton had been considered but deemed to pose no conflict, and the appointment to temporary voting status for Drs. Francis, Gulya, Hood, Roeser, and Canady. Dr. Patow read the panel the charge of confidentiality and stated that the panel was to consider a premarket approval application (PMA) for an auditory brainstem implant.

OPEN PUBLIC HEARING

Gail Umphrey, a recipient of the implant whose way was paid by the sponsors, spoke about her experience with the implant, which she received in 1994 after two years of total deafness. She stated that the device was "a miracle" which had "brought her life back."

Donna McLaughlin, a recipient of the implant whose way was paid by the sponsors, spoke about her experience with the implant, which she received a year ago after two months of total deafness. She noted problems with the facial nerve, taste buds, and so forth, but said that she had "received a miracle" for which she would always be grateful.

Henry Ilecki of the American Speech-Language-Hearing Association discussed auditory brainstem implants (ABI), saying that preliminary indications suggest that ABI recipients generally receive benefits of sound detection and discrimination that

are similar to those afforded by the first generation of cochlear implants. He recommended four areas of investigation for the FDA: perceived disability and quality of life for implant recipient; compatibility with existing hearing assistive technology, especially of the alerting variety, candidacy and screening, and audiological rehabilitation. He concluded that the FDA should continue to recognize and promote the value of a concomitant audiological component to ensure the eventual clinical acceptance, utility, and successful outcomes of ABIs.

OPEN COMMITTEE DISCUSSION

Division Update

Nancy Brogdon, Acting Director of the Division of Ophthalmic and Ear, Nose and Throat Devices Branch, gave the division update. She noted that **Dr. A. Ralph Rosenthal, the Division Director**, is temporarily working on Health Care Financing Administration issues in the Office of Device Evaluation (ODE), and she introduced **Dr. Bernard Statland, the new Director of ODE**. She announced that the Chief of the Ear, Nose and Throat Devices Branch and former Panel Executive Secretary Harry Sauberman was also working in ODE on special projects including partnerships with other countries. She introduced **Dr. Morris Waxler, Acting Chief of the Ear, Nose and Throat Devices Branch** and the ENT Branch's new reviewer, audiologist **Dr. James Kane.**

Ms. Brogdon noted that there were three ENT Panel members were finishing their terms. As she had presented a letter of appreciation from FDA Commissioner Dr. Jane Henney and a recognition plaque to two of the panel members, Drs. Gayle Woodson, and

industry representative, Dr. William Duffell, Jr. on the previous day, she made the same presentation to Dr. Clough Shelton.

Dr. Morris Waxler, Acting Chief of the ENT Devices Branch, gave the branch update, in which he introduced branch personnel.

PMA P000015—COCHLEAR CORPORATION – NUCLEUS 24 AUDITORY BRAINSTEM IMPLANT (ABI) SYSTEM

Sponsor Presentation

Ronald E. West, president of Cochlear Corporation, introduced the device and reviewed the history of the auditory brainstem implant (ABI) project since 1979. He thanked the panel for its consideration and the Office of Orphan Devices for its financial support.

Patti L. Arndt, clinical studies manager, gave an overview of the submission, saying that the device was intended for use in those 12 years old or older, diagnosed with Neurofibromatosis Type 2, with implantation during or subsequent to tumor removal. She listed device components and explained their function. Submission was based on safety and effectiveness data from a U.S. clinical trial on 90 patients and a European clinical trial on 27 patients, extensive laboratory testing, and clinical validation of the implant's components. She discussed the evolution of the ABI systems from the Nucleus 22 to Nucleus 24 devices.

Dr. Martyn Hyde of the University of Toronto discussed experimental design and statistical methods. The trial was a single-subject, repeated-measures design replicated in 60 subjects. Of a total of 92 patients, safety data were provided by 90 subjects and effectiveness based on 60 subjects from 8 sites. Two patients died from unrelated causes;

13 had no auditory percept on activation; and data were unavailable on 17. Standard descriptive/inferential methods were used to detect and quantify treatment effects on the effectiveness cohort of 60, which was considered representative of the target population. Outcome measures included sound detection and speech recognition tests, lip-reading enhancement tests, subjective performance ratings, and subjective benefit ratings at six months. Dr. Hyde explained the statistical methods and the power used and concluded that the study sample is both representative and sufficient, the statistical approach and methods are valid and appropriate, and the claims are conservative and fully supported by data.

Dr. Derald Brackmann of the University of Southern California discussed device safety and surgical complications. He described the implantation procedure and position of the implant, noting that there is substantial device experience for safety. Dr. Brackmann delineated the 22 minor surgical complications and the six device-related complications, as well as the 2 major surgical complications, giving incidence rates for each category. He concluded that of the 90 patients, there were 28 complications in 26 patients, 14 of which were non-stimulations. All but two complications were classified as minor and they were all resolved with reprogramming or a minor modification of the device. The non-stimulators remain a problem. In European safety data on 27 patients, there were no major complications attributed to the ABI and no ABI – related neurological changes. There were no life-threatening, hazardous, or permanent side effects. These results are consistent with U.S. experience.

Dr. William Hitselberger looked at device safety in terms of neurological results. He explained Neurofibromatosis Type 2 and the neurological evaluation used to assess long-term neurological function after implantation. He explained the method and variables

used and concluded that there were no reported ABI-related changes for 80 ABI recipients on 8 different indicators of neurological function or overall neurological status.

Kaira A. Ebinger, senior clinical specialist, looked at device effectiveness. She reviewed subject selection criteria and showed study demographics on age and side of implantation and gender. She explained the clinical trial protocol, which included postoperative evaluations of speech perception, audiological testing, neurological evaluation, and patient questionnaires. Ms. Ebinger looked at auditory performance by group means, CID sentence scores, on sound alone, group means scores on lip-reading enhancement, and CUNY sentence scores over time and in group means. She also looked at European effectiveness results and showed European study demographics. European results were assessed for auditory benefits in terms of environmental sound recognition, closed-set word recognition, open-set sentence understanding for a few, and lip-reading enhancement. Performance questions were also administered to assess device use, speech processor control settings, functional benefit, and perceived helpfulness. She looked at daily device use and showed mean ratings on most and least helpfulness in specific situations. Patient questionnaire results showed that ABI offers significant improvements in many listening situations and recipients are satisfied with ABI and the benefits they receive.

Patti Arndt listed the materials submitted to FDA and read the proposed labeling. Clinical study results were described as they appear in the package insert, with empirical data summarized in the following claims areas: identification of environmental sounds, lip-reading enhancement, open--set sentence recognition, and questionnaire results. Ms. Arndt also summarized the proposed requirements for postmarket training, which include

physicians experienced in tumor removal and cochlear implant surgery, as well as a team approach. Manufacturer-sponsored training would be provided for the implanting physician and ABI team, and an experienced surgical consultant, designated by the manufacturer, must support each physician's first ABI surgery. Ms. Arndt stated that the sponsor did not recommend a postmarket surveillance program because the safety issues are well characterized and longitudinal data support stability of the effectiveness outcomes.

Panel Questions to the Sponsors

Panel questions dealt with clarification of the claims and labeling about the effect of MRI on the device and about the device magnet. Questions also involved time in the operating room, satisfaction results, results on the nonstimulable patients and the two deaths, which might have been surgically related but not necessarily device related.

FDA Presentation

Acting Chief of the ENT Devices Branch Dr. Morris Waxler introduced PMA team leader **Ms. Teri Cygnarowicz**, who introduced the review team.

Dr. I. Sidney Jaffee gave the clinical review, briefly summarizing the history of ABI and listing the device components. He discussed animal studies done on primates, noting no significant adverse reactions in the cochlear nucleus brain tissue. After explaining surgical procedures, he discussed major complications during the safety study on 92 patients. These complications included extrusion, necrosis, dizziness, and blurred vision in low numbers. He also summarized patient results from the effectiveness study on 60 patients. Dr. Jaffee read the contraindication, warnings, and precautions and explained them. In conclusion, he stated that no device-related neurological complications occurred,

that medical surgical and device-related complications were characteristic of cochlear implantation and/or acoustic tumor removal and all were closed or resolved, and that the majority of patients receive benefit from the ABI. He concluded that there is potential benefit for patients without much additional risk.

Dr. James Kane provided the audiological review. He described the efficacy study limitations, which provided no data on 30 of the 90 implanted subjects, and the difference between European and U.S. protocols. He showed the ABI group efficacy data on environmental sound recognition and on stress pattern perceptions, as well as closed-set word identification in various formats. He concluded that all ABI systems provide beneficial acoustic information via electrical stimulation, and the increased number of electrodes provides other benefits. Dr. Kane also read the questions for panel review.

Panel Questions to the FDA

Panel questions involved the best method for inclusion of the data on nonstimulable patients in the labeling in various formats and whether U.S. and European data showed performance of the device above chance levels.

Additional Comments from the Sponsors

The sponsors provided additional information on identification of environmental sounds and clarified that they recommended training but did not require it. They also explained their rationale for explaining the data on nonstimulable patients, which was first to show the chance that the device would not work at all and then to show the results for those who do stimulate within certain parameters.

Primary Panel Reviews

Dr. Gayle Woodson described the device in both the Nucleus 22 and 24 systems and concluded that it is reasonable to use the data submitted in judging the safety and efficacy of the Nucleus 24. She thought that the data presented support the conclusion that the implantable brainstem stimulator restores auditory sensations in patients who are deaf after bilateral removal of eighth nerve tumors. The risks are essentially the same as the surgery to remove the tumor, and thus the benefits exceed the risk and the device provides a real opportunity to hear for those who otherwise could not.

Dr. Paul Kileny reviewed the background of the PMA, described the device, and summarized relevant data. He recommended that the data provided in the PMA be accepted in support of the request for approval of the Nucleus 24 system in spite of the fact that the U.S. study was conducted on the Nucleus 22 System. He also concluded that the moderate hearing benefit for the neurofibromatosis Type 2 patients provided by the ABI system does exceed the risk of implantation. He recommended that the PMA be recommended as approvable subject to six conditions, which he outlined. These dealt with verification of patients with no auditory percept and revision of efficacy information to include such data in a manner appropriate with single subject, binomial design, provision of preoperative audiological information on the patients, revisions to the surgeon's manual, and a two-year period of postapproval studies.

Panel Discussion of FDA Questions

The panel agreed that the use of the efficacy data from the Nucleus 22 ABI System to support approval of the Nucleus 24 ABI System was appropriate. The panel also agreed that the hearing benefit from this device for the Neurofibromatosis Type 2 patient

exceeds the risk of implantation. Panel members discussed the presentation of the efficacy data at some length. They agreed that the device should come without the magnet and that the surgeon would have to insert the magnet if desired. The panel thought that the contraindication on use with a gamma knife is overstated and should be reworded as a precaution, and that a strong recommendation rather than a requirement on surgical training should be included. An option should be included in the surgeon's packet information about implantation of one or two implants at the same time, although it was also noted that there are no efficacy data on bilateral implants and that these may be clinical judgment questions. Postapproval studies were not recommended, although it was suggested that some proof of efficacy over time would be useful and could be established by mailing in a response card. It was agreed that a nonstimulable device is not a failed device. It was also suggested that all therapeutic claims should be reworded to state the percentage of those implanted who then received auditory stimulation and of those receiving stimulation, the percentage of those who received therapeutic benefits claimed. It was also suggested to remove the fractions and use only percents. The panel recommended that instructions on neurological monitoring should be amplified in the surgeon's manual.

OPEN PUBLIC HERAING

There were no requests to speak.

FDA CLOSING COMMENTS

FDA representatives had no further comments.

SPONSOR CLOSING COMMENTS

Sponsors thanked the FDA and the panel for the excellent review and their

concern, time, and effort. They noted that this device represents a small fraction of their device sales; the real issue is device availability to patients in need.

PANEL RECOMMENDATIONS AND VOTE

Panel Executive Secretary Sara Thornton read the voting options and instructions.

A motion was made and seconded to recommend the PMA as approvable subject to conditions. The conditions were as follows:

1) The first claim should be revised to indicate that of the 90 patients implanted with the ABI, 82% perceived sound upon stimulation.
2) All claims should be simplified by eliminating fractions of patient numbers and chance percentages. The phrase "of those patients who stimulated" should be added to all claims.
3) The device should be delivered without the magnet in place, and appropriate modifications should be made to the surgeon's manual.
4) A statement should be added that the additional efficacy of bilateral simultaneous implantation has not been studied.
5) Information on neurophysical monitoring should be amplified in the surgeon's manual, and recommended training should include more specific guidelines on neurological monitoring and neurological events that may occur during ABI placement.
6) A precaution should state that caution should be used in individuals who have undergone radiotherapy with use of gamma knife because of possible injury to the cochlear nucleus.

7) Labeling should indicate that it is strongly recommended that the implantation team should receive training in techniques for appropriate implantation.

8) The presentation of the efficacy data in the patient information packet should clearly indicate the percentage of patients who did perceive sound.

(A motion that the sponsor should carry out limited postmarket surveillance on existing patients via a questionnaire on continuing auditory stimulation over a two-year period did not carry with a second.)

The motion to recommend the PMA as approvable subject to the above eight conditions carried unanimously. Panel members stated that they voted to recommend the device as approvable because NF2 is a devastating disease and the device would be helpful. They found the efficacy data easily interpretable and convincing and the patients' perspective useful. They thanked both sponsors and patients. The Industry Representative thanked the FDA and the review team for a collegial effort and noted that the least burdensome approach includes the rapid conclusion of the approval process.

Ms. Brogdon stated that the FDA is committed to bring this device to a quick review and thanked the panel. Ms. Thornton noted that the September 22 meeting of the ENT Panel has been cancelled and that a schedule for 2001 will be forthcoming. Panel Chair Dr. Patow thanked sponsors, panel, and FDA staff and adjourned the Open Session at 3:15 p.m.

I certify that I attended the Open Session of the Ear, Nose and Throat Devices Panel Meeting on July 20-21, 2000, and that this summary accurately reflects what transpired.

Sara M. Thornton
Panel Executive Secretary

I approve the minutes of this meeting as recorded in this summary.

Carl A. Patow, M.D.
Panel Chair

Summary minutes prepared by

Aileen M. Moodie
9821 Hollow Glen Pl.
Silver Spring, MD 20910
301-587-9722